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Division of Dockets Management (HFA-305)
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October 24, 2005

Re: Docket No. 05N-0311
Critical Path Initiative; Developing Prevention Therapies - Workshop Planning

As a member of the Pharmaceutical Research and Manufacturers of America (PhRMA), Abbott acknowledges the PhRMA letter filed to this docket proposing a two-part workshop. Abbott provides the following information in order to directly reply to select questions that were published in the *Federal Register* on August 3, 2005.

Question 6. Are there specific regulatory concerns in developing chemopreventions? What steps can FDA take to facilitate development in this area such as:
a. Mechanisms to streamline the regulatory process

FDA might consider offering a specific pathway to promote the development of preventive therapies. For example, modify the subpart H pathway (or come up with another subpart) for these kinds of products. Currently, the "letter of the subpart H regulation" makes it applicable for TREATMENT of serious or life-threatening diseases and there must be meaningful benefit over existing therapies. It is possible that the approval of chemoprevention agents could be based on surrogate endpoints or biomarkers that, like current subpart H, would necessitate confirmatory clinical evidence (e.g. long term follow-up observation). Therefore, following a model like subpart H to allow chemopreventives to be approved on the basis of surrogates with a requirement for confirmation may be worth considering. Phase 4 commitments could include long-term use trials via registries with DSMBs overseeing safety.

Question 2. Which diseases are the most promising with regard to development of chemoprevention therapies?

Diseases that involve deficiencies in the production of naturally occurring substances (e.g. hormones, growth factors, enzymes, etc.) have historically been treated with replacement therapies allowing patients to lead relatively healthy lives. Such treatment has delayed the onset of serious disease.

Question 7. What are some of the obstacles facing manufacturers who wish to develop new or existing compounds for chemoprevention?

- Innovators develop products that are taken chronically and patients have additional choices when generic versions become available. It is critical to establish the efficacy and safety profile of all products taken long-term. Should this burden be shared between the innovator and generic companies?

- In order to conduct long-term prevention trials, sponsors must be able to weed out persons at risk from long-term treatment and enroll a lower risk population for the duration of the trial. This may require a personalized medicine approach to differentiate at-risk vs. lower-risk populations.

- Historically, FDA allowed cholesterol lowering claims to support CV outcomes claims based on tracking the association of a laboratory value to improved CV outcome over years. This model works. Yet it begs the question of how to treat next-in-class products. If Product X works on the lab value, is Product X automatically entitled to the outcomes claim? How much data are needed vs. how much similarity among products to merit the same claim?

- Sponsors who wish to develop preventive agents based on surrogate markers are faced with years of work to validate a surrogate. How does this impact the patent life of the compound? Is it worth it for industry to validate the surrogate? Are there ways to extend patent life to encourage the lengthy investment in developing chemopreventive agents?

Breakout Session - Cardiovascular prevention issues

a. What characteristics of cardiovascular disease make prevention promising?

There are well-documented risk factors, such as elevated triglycerides and lipids, obesity, hypertension, and smoking. We need prospective data to demonstrate that pharmacologic intervention to modify risk factors has a long-term effect on CV mortality and morbidity.

- Modest weight loss (approx. 5-10 lbs) has been associated with lowering CV risk. If weight loss derived from dietary changes and increased exercise is helpful, might the addition of pharmacologically induced weight loss be even more beneficial? Can weight loss serve as a surrogate for lowering CV risk in at risk populations?
- NCEP ATPIII defined plasma levels of triglycerides (TGs) >150 mg/dl as elevated and HDL-C levels <40 mg/dl as low. Both TGs and HDL-C are independent risk factors of CHD risk.
- In addition, Laws and Reaven showed that high TGs and low HDL-C when expressed as a ratio, are indicators of insulin resistance, also a CV risk factor.
- Diabetic patients and other insulin-resistant populations tend to have high TGs and low HDL-C levels. Although low-density lipoprotein cholesterol (LDL-C) levels are not substantially raised, the LDL particle is often modified to be smaller and denser than in similar non-diabetic populations and is considered to be a more atherogenic state.
- ATP III does not specify a goal for HDL-C or TGs; however, clinical trial data suggest that raising HDL-C will reduce risk. Drugs for raising HDL-C and lowering TGs (fibrates and niacin) are recommended in patients with elevated TGs (>200 mg/dl) and low HDL-C to achieve non-HDL-C goals in subjects with diabetic dyslipidemia or features of the Metabolic Syndrome.
- Fenofibrate produces HDL cholesterol elevation of 10-20% together with large reductions of 30-40% in plasma TGs. In addition, a 15% reduction in plasma fibrinogen is commonly observed. Fenofibrate also reduces plasma levels of several cytokines and markers associated with vascular inflammation such as C-reactive protein, now recognized as a risk factor for the development of atherosclerosis. Fenofibrate equally modifies the quality of the lipoprotein particles with a shift on LDL mass distribution to particles of larger size and buoyant density.

b. What characteristics from epidemiologic, early trials, or other models make particular drugs promising?

- Drugs that induce weight loss have been associated with lowering CV risk directly and via secondary benefits in addition to weight loss. For example,
    - the SCOUT (Sibutramine Cardiovascular Outcomes) trial, underway in Europe, is a randomized, double-blind, placebo-controlled trial examining the incidence of fatal and nonfatal CV outcomes in approximately 10,000 obese patients at high risk for CV disease treated for up to 5 years with diet and exercise plus sibutramine or placebo. When completed this study will provide precise estimates of the relative benefits and risks of sibutramine when added to lifestyle modification in a population for whom sustained weight loss is highly desirable.
    - the STORM (Sibutramine Trial of Obesity Reduction and Maintenance) trial, the longest study of sibutramine published to date, included approx. 250 patients who completed the 2 year trial. Sibutramine-associated weight loss was accompanied by significant reductions in serum triglycerides, VLDL, cholesterol, insulin, C-peptide and uric acid, as well as clinically meaningful increases in HDL. This study demonstrated that sibutramine provides a number of secondary benefits in addition to weight loss.
- The Helsinki Heart Study (HHS), testing long-term use of a fibrate (gemfibrozil) in 4081 hypercholesterolemic men without prior coronary disease, showed that gemfibrozil led to a substantial reduction (34 %) in total CHD. This result was subsequently reinforced by the results of the Veterans Affairs High-density lipoprotein Intervention Trial (VA-HIT), carried out in 2531 male patients (-22%). However, a subgroup of diabetic patients had a greater reduction in CVD events (-32%).
- The results of the angiographic trial DAIS (Diabetes Atherosclerosis Intervention Study) showed a reduction of coronary artery disease progression in patients with type 2 diabetes with moderate dyslipidemia after at least three years of fenofibrate treatment.
- In a post-hoc analysis of the Bezafibrate Infarction Prevention (BIP) study, bezafibrate significantly reduced coronary events and strokes only in patients with features of the Metabolic Syndrome.
- The FIELD Study (Fenofibrate Intervention and Event Lowering in Diabetes) was designed to provide the first properly randomized evidence as to whether the substantial effects of fenofibrate on HDL-C and TGs conferred any independent clinical benefit additional to any direct benefits that might be offered by a lowering of LDL-C.
    - FIELD is a five-year, double-blind, randomized trial involving 9795 patients, ages 50-75 years old, with type 2 diabetes mellitus and with baseline total cholesterol between 115 mg/dl and 250 mg/dl.
    - FIELD was designed to assess the efficacy and safety of fenofibrate in reducing the risk of both fatal and CHD in patients with type 2 diabetes.
    - The results of FIELD will be presented at the AHA late-breaking session on November 14th 2005.

<u>Early Detection of Disease for Prevention</u>:

- The use of anatomic surrogate endpoints of Coronary Artery Disease, like Intravascular Ultrasound (IVUS) and Carotid Intima-Media Thickness (cIMT), have been validated in prospective studies as being predictive of cardiovascular events. These studies detect

vascular atherosclerotic disease early in the disease process and with great precision. Trials based on these two methods are considerably shorter and less onerous than outcome trials. How can we leverage the use of these endpoints to approve therapies for prevention of CAD?

- In 2003, the Centers for Disease Control (CDC) and the American Heart Association (AHA) published a joint statement that recommends the use of hs-CRP as an independent marker to assess risk of recurrent CHD events in patients with stable CAD or acute coronary syndromes. How can we use this marker to approve drugs for the primary prevention of CHD risk?

Abbott is pleased to contribute this information and to assist with workshop planning, particularly for the cardiovascular therapeutic breakout sessions.

Should you have any questions, please contact Ms. Lauren Hetrick, Senior Director, Regulatory Intelligence/FDA Liaison Office at (301) 255-0080.

Sincerely,

Douglas L. Sporn
Divisional Vice President